UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,842	11/17/2000	Roger Briesewitz	STAN-131	8224

7590 05/07/2002

Bozicevic Field & Francis LLP
Attn Bret E Field
200 Middlefield Road
Ste 200
Menlo Park, CA 94025

EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	10

DATE MAILED: 05/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/716,842	Applicant(s) BRIESEWITZ ET AL.
	Examiner " Neon" Phuong Huynh	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *1-15,37 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-38 are pending.

2. Claims 1-15 and 37-38 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. In view of the amendment filed 01/30/02, the following rejections remain.

4. Claims 16-36 stand rejected under 35 U.S.C. 102(b) as being anticipated by the WO 95/10302 publication (April 1995, PTO 1449) for the same reasons set forth in Paper No 8.

Applicants' arguments filed 1/30/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the drug is present as a conjugate with a ligand where the this ligand is referred to in the claims as a targeting moiety; (2) the WO95/10302 publication does not teach administration of a drug "as a conjugate" with another ligand for the purpose of modulating the biodistribution of the drug; (3) applicants acknowledge that this WO95/10302 publication does discloses approaches for modifying the distribution of drugs or toxins present in the blood stream of an individual by administering bifunctional molecules to the individual. However, the bifunctional molecules do not include the drug whose distribution is to be modified as part of the molecule and (4) the claims 19, 24-26 and 36 are specifically directed to targeting a drug to an "intracellular space" since the ligand component of the bifunctional molecule is limited to a ligand for an intracellular protein.

However, Applicants argue the limitation "intracellular space" which not recites in the claims. Further, the WO 95/10302 publication teaches a method of modulating the biodistribution of a drug by administering to a mammalian host, a bifunctional molecule consisting of a drug moiety such as opiates (See page 13 line 12) **either covalently or non-covalently linked** which is conjugated (see page 13 lines 32-35 to a targeting moiety such as serum albumin, transferin, ferritin which are extracellular proteins, steroid binding protein which is intracellular protein, thyroxin binding protein (See page 3 lines 22-25, page 9 lines 4-7, in particular) or steroid such as estradiol wherein the targeting moiety "will be selected to bind to its complementary binding member", for example, the targeting moiety albumin will bind to the

albumin ligand which is an extracellular protein, the transferin will bind to the transferring receptor which is also an extracellular protein, the steroid will bind to the steroid binding protein which is an intracellular protein and a small molecule (See page 10, lines 35-36, in particular). The WO 95/10302 publication further teaches that the bifunctional molecule exhibits enhanced efficacy of the drug upon administration to the host because the relative long half life of the targeting protein mentioned above which extend the half life of the drug in circulation and one can also modulate the ultimate sites or (target the drug) and volume of distribution of the bifunctional molecule based on location, distribution of the targeting molecule (See page 10 lines 1-21, in particular). The bifunctional molecule is either connected by covalent bonds (without linking group) or non-covalent linkage via monoclonal antibodies or fragments thereof such as Fv, Fab, $F(ab')_2$ (See page 13 lines 32-35; page 14, line 20-23; page 15 lines 1-2, in particular) or via linking group (See page 18 lines 26-36, in particular). The bifunctional molecule exhibits reduced toxicity upon administration to the host by modulate the distribution of a drug such as opiate to the CNS or cocaine to be excreted (See page 33 line 26, in particular) or extend the life-time of the drug by conjugated to serum albumin or Fc of the immunoglobulin (See page 33 line 10) or to facilitate the clearance of the drug from the blood stream or to extend the stimulation of an immunogen (See abstract, in particular). The drug target opiate receptor is a protein and the drug is targeted to an extracellular site since the opiate receptor is located extracellular site of a mammalian host which is also the endogenous biodistribution modulating extracellular protein.

While the reference is silence with regard to compared the drug to a free drug control, it is inherent to compare to the control in order to establish the effectiveness of the biodistribution of the drug. The bifunctional molecule has a molecular weight of less than about 5000 Daltons since the targeting moiety has a molecular weight of about 200 D to less than about 1000 D and the molecular weight of the drug (opiates) has a molecular weight of about 3000 D and the sum of both is less than about 5000 Daltons (See page 20 lines 29-33, in particular). Thus, the reference teachings anticipate the claimed invention.

5. Claims 16-36 stand rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No. 5,843,440 (Nov 1998, PTO 1449) for the same reasons set forth in Paper No 8.

Applicants' arguments filed 1/30/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the drug is present as a conjugate with a ligand where the this ligand is referred to in the claims as a targeting moiety; (2) the WO95/10302 publication does not teach administration of a drug as a conjugate with another ligand for the purpose of modulating the biodistribution of the drug; (3) applicants acknowledge that this WO95/10302 publication does discloses approaches for modifying the distribution of drugs or toxins present in the blood stream of an individual by administering bifunctional molecules to the individual. However, the bifunctional molecules do not include the drug whose distribution is to be modified as part of the molecule and (4) the claims 19, 24-26 and 36 are specifically directed to targeting a drug to an "intracellular space" since the ligand component of the bifunctional molecule is limited to a ligand for an intracellular protein.

However, Applicants argue the limitation "intracellular space" which not recites in the claims. Further, the '440 patent teaches a method of modulating the biodistribution of a drug by administering to a mammalian host, a bifunctional molecule consisting of a drug moiety (Fab fragment of anti-cocaine antibody) (See Abstract, column 2, lines 2-9) **linked (conjugated) to a targeting** moiety such as albumin or steroid such as vitamin D, or the Fab fragment of anti-erythrocyte that binds specifically to erythrocyte (See column 2, lines 41-67 bridging column 3 lines 1-10, in particular). Upon administering the bifunctional molecule to the patient, the targeting moiety such as the albumin will bind to the endogenous biodistribution modulating protein such as the albumin ligand which is an extracellular protein. The targeting moiety such as Vitamin D will bind to the endogenous biodistribution modulating protein such as the steroid binding protein which is an intracellular protein. The targeting moiety such as the Fab fragment of anti-erythrocyte will bind to erythopoietin on the erythrocyte wherein the erythropoietin is an endogenous biodistribution modulating protein. The bifunctional molecule is either connected by covalent bonds (without linking group) or non-covalent linked via monoclonal antibodies or fragments thereof such as Fv, Fab, $F(ab')_2$, (See column 8 lines 10-13; column 6 lines 27-31, in particular) or via a linking group such as a sulfhydryl group (See column 8, lines 45-57, in particular). The bifunctional molecule has a molecular weight of less than about 5000 Daltons. The '440 patent further teaches that the therapeutic methods are applicable to a broad range of target agent such as Fab fragment of anti-RBC conjugated to a Fab fragment of anti-cocaine to reduced toxicity of the cocaine upon administration of to a host (See column 3, lines 11-12, column 11, lines 11-in particular). The '440 patent also teaches a method of extending the lifetime of the bifunctional molecule in the blood stream (thereby enhance efficacy) by linking

the antibody binding fragment (Fv) that binds specifically to erythrocytes or albumin to a second targeting agent such as antibody fragment that binds specifically to targeting agent or drug (See claims 1-8 of '440, in particular). The bifunctional molecule is a pharmaceutical composition to be administered parenterally, intravascularly, intramuscularly, subcutaneously, or by transfusion (See column 9, lines 6-26, in particular). While the reference is silence with regard to compared the drug to a free drug control, it is inherent to compare to the control in order to establish the effectiveness of the biodistribution of the drug. Thus, the reference teachings anticipate the claimed invention.

6. Claims 16-36 stand rejected under 35 U.S.C. 103(a) as being unpatentable over the WO 95/10302 publication or US Pat No. 5,843,440 (Nov 1998, PTO 1449) each in view of US Pat No. 5,830,462 (Nov 1998, PTO 1449) for the same reasons set forth in Paper No 8.

Applicants' arguments filed 1/30/02 have been fully considered but are not deemed persuasive.

Applicants' position is that since the primary references are fundamentally different from the claimed methods and they do not teach or suggest administering the drug itself as a bifunctional molecule.

However, the primary references teach bifunctional molecule as a pharmaceutical composition to be administered parenterally, intravascularly, intramuscularly, subcutaneously, or by transfusion. The teachings of the WO 95/10302 publication and the '440 patent have been discussed supra.

The reference teachings differ from the claimed invention only by the size of bifunctional molecule.

The '462 patent teaches that a targeting moiety using a ligand such as FK506 that are small in size and binds to the endogenous biodistribution modulating protein such as peptidyl prolyl isomerase (FKBP12) which is an intracellular protein (See column 22, lines 62-64, in particular). The '462 patent further teaches other targeting moiety such as cyclosporin A that binds to the cyclophilin receptor, the estrogen that binds with the estrogen receptor, the vitamin D that binds to the vitamin D receptor with high affinity (See column 22 lines 66-67 bridging column 23, line 1-27). The reference targeting moiety such as FK506 is typically being at least about 150 D and few than about 5 kD, usually fewer than about 3 kD (See column 22, lines 62-64, in particular). The '462 patent teaches a bifunctional targeting domain such as FKBP12

ligand fused to a tryrosine kinase CD3ζ (See Fig 2, in particular) or FK506 fused to DNA binding domain (Gal4) (See Abstract, Fig 2, column 17, line 14; column 21 line 23-26, in particular) or Fas antigen receptors that is linked to FKBP12 which is capable of binding to the FK506 type moiety (See column 23 lines 17-20, claims 34-42, 47-51 and 109-112 of '462, in particular). The '462 patent further teaches that these moiety are linked together through a linking group (See column 24, lines 17-24, column 25, line 28-35, in particular). The '462 patent further teaches a pharmaceutical composition (See column 6, line 63-67 bridging column 7 lines 1-16, in particular). The '462 patent also teaches chimeric protein can be target to a specific location by adding a signal sequence from the vesicle or golgi or ER, for example.

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the albumin targeting moiety as taught by the WO 95/10302 publication or the antibody fragment of Erythrocyte targeting moiety as taught by the '440 patent with the FK506 or FKBP12 or cyclosporin A that binds to the cyclophilin receptor, or the estrogen that binds with the estrogen receptor, or the vitamin D that binds to the vitamin D receptor which all bind with high affinity as taught by the '462 patent. The '462 patent teaches targeting moiety such as FK 506 that binds to the endogenous biodistribution modulating intracellular protein such as FKBP12 and vice versa for a method of modulating the biodistribution of a drug upon administering to a host. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. While the reference is silence with regard to compared the drug to a free drug control, it is within the purview of one ordinary skill in the art to establish the effectiveness of a drug by comparing to the control.

One having ordinary skill in the art at the time the invention was made would have been motivated with a reasonable expectation of success to substitute because the '462 patent teaches that targeting moiety such as FK506 binds to FKBP12 with high affinity (See column 22 lines 66-67 bridging column 23, line 1-27).

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

10. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
May 6, 2002

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600